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# Peripheral Nerve Injury and Current Treatment Strategies

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Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/intechopen.68345>

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## Abstract

Neuronal cells are the main fundamental anatomic unit of the system. Nerve injuries are generally divided into three categories as neuropraxia, axonotmesis and neurotmesis. Neurotmesis is the most severe form. Schwann cells are activated within 24 hours of the injury and the healing cascade continued with the cells, which are stimulated by Schwann cells. And neurotrophic factors like nerve growth factor (NGF) have a crucial role in regeneration and degeneration processes. Additionally, Schwann cells upregulate the expression of some proteins, such as fibronectin, which are crucial for axonal regeneration. All this information about nerve healing sheds light on treatment studies. Iatrogenic nerve injury has an important place in peripheral nerve injury. Causes may be direct surgical damage, wrong intraoperative patient positioning, anaesthesia-related reasons or limb tourniquets. Typical symptoms are motor or sensory deficits such as paraesthesia, weakness, paralysis and pain. Many of the traumatic nerve injuries require surgical repair. Direct nerve repair and autologous nerve grafts are still gold-standard treatment options. Additionally, nerve conduits are very successful to provide an ideal peripheral support for neuronal recovery but are still insufficient. In recent years, research efforts have focused on the neurotrophic factors and cell-based therapies to perform better microenvironment for neuronal healing.

**Keywords:** peripheral nerve, injury, iatrogenic, nerve grafts, conduit, cell-based therapy

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## 1. Introduction

An injury to a nerve can result in a problem with the muscle innervation or in a loss of sensation. In some people, it can also cause pain. The type of nerve injury will determine the type of treatment that will be needed. Peripheral nerve injuries (PNIs) affect all age groups and have many causes like trauma and medical disorders. The majority of the peripheral nerve injuries

(PNI) occur in the upper extremity and are secondary to trauma [1]. Typical symptoms are motor or sensory deficits such as paraesthesia, weakness, paralysis and pain [2]. Many of the traumatic nerve injuries require surgical repair. The primary goal of the repair is to achieve the reinnervation of the target organs, but the therapeutic options which are used at present cannot achieve perfect sensory and motor recovery in all cases. In this chapter, the pathophysiology and mechanisms of nerve injuries, the traumatic nerve injuries, especially the iatrogenic forms, and therapeutic options for the peripheral nerve injuries will be discussed.

## 2. Peripheral nerve anatomy

Peripheral nervous system consists of neuronal cells, glial cells and stromal cells. Neuronal cells are the main fundamental anatomic unit of the system. Neurons conduct electrical signals between central nervous system and other parts of the body. Afferent neurons carry information from the body to the brain, and efferent neurons carry signals from central nervous system to target organs. Each neuron consists of a cell body, dendrites and an axon. Transportation of the action potential is from cell body through the extension of the body called axons. Cell body is the source of nutritional elements and neurotransmitters. Nerve fibres are categorized into three groups based on their functions (motor, sensory and autonomic neurons) and into two groups according to structural characteristics (myelinated and unmyelinated). Myelin is a critical molecule for conduction of action potential, which is composed of 30% proteins and 70% lipids. Schwann cells (SCs) constitute the major neuroglial component of the peripheral nervous system and surround axons at regular intervals forming the myelin. And there are unmyelinated intersegmental areas known as Ranvier nodes. Ranvier node is enriched with voltage-sensitive sodium channels and generates ionic impulses only at the node. Owing to this structure, action potential jumps from one node to the next along the length of the axon and saltatory conduction occurs. This process results in faster conduction of the action potential in myelinated nerves rather than unmyelinated nerves [3, 4].

Connective support of the neuron consists of three laminary structures including endoneurium, perineurium, epineurium and mesoneurium. The deepest structural layer nearest to the axon is endoneurium, which is composed of collagen fibres. Perineurium surrounds multiple nerve fibres and their endoneuriums. Perineurium is composed of collagen fibres and perineural cells, which provide a protective barrier between the nerve and its blood supply. The entry of large proteins, toxins, antigens and infectious agents is prevented by that barrier (blood-nerve barrier) [3]. Perineurium has a major role in maintaining the integrity and providing tensile strength and elasticity of the nerve [5]. The external layer is the epineurium, which consists of two components. Interfascicular epineurium surrounds each nerve fascicle, and the extrafascicular epineurium invests the entire nerve trunk and clinches the blood vessels to the nerve [4]. The epineurium is a quite strong layer and resists to compression injuries with its collagen fibres and lipid globules. Besides, epineurium is known as the most abundant type of connective tissue of the nerve. Eighty-eight per cent of the sciatic nerve is composed of epineurium at the gluteal level [6]. The outermost tissue around the nerve trunk

is mesoneurium. Mesoneurium harbours anastomoses between veins and arterioles of the nerve. Mesoneurium limits the frictional forces during movement of the nerve against closed local structures [7].

### **3. Grading nerve injury**

The first approach to the nerve injury is grading because that defines the severity of the injury and success of the repair. The most widely accepted grading system, which was defined by Seddon and Sunderland, is according to the microscopic changes secondary to the injury [6, 8].

Seddon divided nerve injuries into three categories as neuropraxia, axonotmesis and neurotmesis. The mildest form of nerve injury is neuropraxia, which is characterized by focal demyelination without damage to nerve continuity. This kind of injury does not cause distal degeneration. Neuropraxia typically occurs after compression or traction of the nerve. The conduction velocity is decreased, but the damage is transient [9]. The complete recovery time of the injury varies from 1 week to 6 months [10]. Axonotmesis is the damage to the axons with focal demyelination where connective tissues (perineurium and epineurium) of the nerve are preserved. Distal axon and myelin degeneration causes complete denervation. Although the motor and sensory function recovery is not as fast as in neuropraxia, preservation of the supportive tissue makes recovery perfect in axonotmesis. The most severe form of the nerve injury is neurotmesis, which is defined as full anatomical and physiological transection of the nerve. All functional components are damaged, and recovery without surgical repair is impossible [11].

Sunderland divided nerve injuries into five categories mostly according to supportive tissue damage [6]. First-degree injury is equivalent to neuropraxia defined as partial disruption in conduction. Second-degree injury is equivalent to axonotmesis. In the third-degree injury, perineurium is left intact, but endoneurium and axon are disrupted. The functional recovery of the nerve depends on the extent of the injury. In the fourth-degree injury, epineurium is the only structure that remains intact. Surgical repair is required for recovery. The fifth-degree injury defines complete transaction of the nerve, and as in neurotmesis, surgical repair is necessary [4].

### **4. Pathophysiological changes after nerve injury**

The injury to the neuronal tissue does not result in mitosis or cell proliferation like other tissues of the human body. First-degree injuries result in mild or no pathological changes. Only decrement of conduction velocity is observed, and none of the regeneration or degeneration processes are activated. However, in the second-degree injury, a unique pathophysiological change defined as Wallerian degeneration occurs in the neural tissue which is not observed in any other tissues [12]. In Wallerian degeneration, a calcium-mediated process results in anterograde degeneration distal to the injury site. Wallerian degeneration ensues 24–48 hours after the injury with fragmentation of distal axons and myelin is formed histologically [13]. Disorganization of

neurotubules and neurofilaments causes irregular axonal margins. Structural axonal durability is lost 48–96 hours after injury and conduction of impulses ceases. Myelin disintegration lags slightly behind that of axons but is well advanced by 36–48 hours [11].

Schwann cells are activated within 24 hours of injury. Their initial role is phagocytosis of the axonal and myelin debris. Macrophages migrate to the injury site and stimulate proliferation of Schwann cells and fibroblasts. Schwann cells and macrophages work together to clean up the injury site which may take 1 week to several months. The other significant role of Schwann cells is to complete the cleaned endoneurial tubes in organized longitudinal columns defined as Bungner's bands. Bungner's bands are important guides for sprouting axons during reinnervation [11, 14, 15].

The third-degree injury (intrafascicular injury) involves retraction of the severed nerve fibre ends due to elastic endoneurium. Local trauma leads to a significant inflammatory response. Fibroblast proliferation aggravates the process, and a dense interfascicular scar forms. This kind of injury impairs axonal regeneration, and endoneurial tubes remain denervated. If the endoneurial tube does not receive a regenerating axon, progressive fibrosis eventually obliterates it. In the fourth- and fifth-degree injuries, activated Schwann cells and fibroblasts cause vigorous cellular proliferation. Local vascular trauma leads to macrophage accumulation. In these injuries, the nerve ends become an irregular mass of Schwann cells, fibroblasts, macrophages and collagen fibres. Regenerating axons reach that disorganized proximal stump and encounter a rough barrier that impedes further growth [11].

Disconnection of cell bodies and axons activates programmed cell death pathway within 6 hours of the injury in a process called chromatolysis [9, 15].

Neurotrophic factors have a crucial role in regeneration and degeneration processes. Macrophages that migrate to the injury site express interleukin-1 (IL-1). IL-1 stimulates nerve growth factor (NGF) production by Schwann cells. NGF is very important for axonal regeneration process and myelin formation [16]. Additionally, Schwann cells upregulate the expression of fibronectin, laminin and neurotrophins, which are crucial for axonal regeneration [11]. All of these factors are not enough for recovery of transected nerves. If the surgical repair fails, denervation of the distal end leads to lack of impulse conduction followed by loss of motor end plates and muscle fibrosis [17].

## **5. Mechanisms of peripheral nerve injury**

There are various mechanisms that lead to peripheral nerve injury. All types of traumatic injury can have an iatrogenic component. Direct nerve damage is one of the mechanisms that may occur during surgery or accidentally secondary to an external trauma. These iatrogenic injuries may be provoked by knives, propellers and scalpels used in surgery or a needle trauma secondary to the anaesthesia technique. Traction injuries may occur during surgery by surgical retractors or wrong positioning of the limbs. Compression injury occurs secondary to wrong positioning of the limbs, poor padding of the body surfaces or use of surgical tourniquets. The pathophysiological mechanisms of compression injury involve both



mechanical compression damage and ischemic damage. Ischemic injury may be caused by surgical tourniquets, prolonged immobility, haematoma surrounding a nerve or vasoconstrictor agents. Injection of neurotoxic drugs is another iatrogenic cause of nerve injury. An additional mechanism involved in peripheral nerve injury is double crush syndrome. Patients who have medical comorbidities (e.g., diabetes mellitus, rheumatoid arthritis) associated with peripheral neuropathy have more sensitive nerves and are more susceptible to a secondary damage like compression or laceration. A minor injury may cause permanent nerve injury in these patients. Patients with features such as diabetes mellitus, obesity, peripheral vascular disease, arthritis, alcohol usage, tobacco usage, advanced age, circulatory failure, extreme weakness are more likely to have nerve damage in the perioperative period [18–30].

There are also other risk factors which are independent from patients. Neurosurgery, cardiac surgery, gastrointestinal surgery and orthopaedic surgery are associated with a higher incidence of peripheral nerve injury. Perioperative risk factors include hypovolemia, hypotension, hypoxia, electrolyte disturbances, hypothermia, length of surgery (>2–4 hours) and patient positioning [19, 21, 31–35]. General anaesthesia and neuraxial blockage have a risk for peripheral nerve injury because they limit patients' own position changes as compared to mildly sedated patients.

## 6. Causes of iatrogenic nerve injury

In one study, 17.4% of the traumatic nerve injury cases ( $n = 722$ ) surgically treated in a tertiary care service were iatrogenic in origin. And 94% of them occurred during a previous operation [36]. In an extensive retrospective study spanning a period of 10 years, the frequency of perioperative peripheral nerve injuries was 0.03% [37]. When operated nerves were examined individually based on surgical specialty, 25% of the operated sciatic nerve injuries, 50% of the operated femoral nerve injuries and 93% of the operated accessory nerve injuries were found to be caused by iatrogenic injuries [38–40].

Iatrogenic nerve injury may be associated with operational or nonoperational factors. Needle injections and external compressions are common nonoperational causes. Operational factors may be directly related to surgery or may involve wrong patient positioning. Direct intraoperative injury mechanisms include cutting, crushing, tying off, penetrating, twisting by screws, stretching by retractors, grabbing or squeezing by repositioned bone, coagulating with cautery or bipolar forceps, burning by cement or excision of the target pathology. It was reported that 94% of the iatrogenic peripheral nerve injury operations were caused by direct surgical damage [36, 41–43].

Nerves cannot always be clearly visualized in the operative field. There are reports that they have been mistakenly recognized as a tendon or vessel [44–47]. And sometimes nerves may be removed during nerve sheath tumour or lymph node excision (accessory nerve may be damaged during lymph node dissection from posterior triangle of the neck).

Nerve sheath tumours are another surgical risk factor for nerve injuries because they are rarely truly recognized and approached. They may be diagnosed as an unspecified lump, undetected tumour or ganglion, so the surgical interventions may result in disappointment.

Nerve sheath tumours are mostly of benign nature (schwannoma or neurofibroma), and appropriate surgical interventions are able to correct neurological deficits [48].

In order to avoid such outcomes, surgeons must have extensive anatomic knowledge about peripheral nerves and be experienced in specialized surgical intervention.

### **6.1. High-risk surgical procedures**

In addition to all other external factors, certain surgeries carry a high risk for peripheral nerve injury. Common procedures that may cause nerve injury are osteosynthesis, osteotomy, arthrodesis, lymph node biopsies from the posterior triangle of the neck, carpal tunnel release, Baker's cyst excision, varicose vein surgery and inguinal hernia repair [41].

A study reported that the most common surgical interventions associated with peripheral nerve injury are as follows in decreasing order: 45% major procedures (orthopaedic procedures, abdominal surgery and trauma), 27% minor procedures (lymph node surgery and varicose vein surgery), 15% neurosurgical interventions (carpal tunnel operations and tenolysis), and 4% non-surgical interventions (arterial or venous puncture and plaster cast) [36, 41].

### **6.2. Anaesthesia and peripheral nerve injury**

Anaesthesia has a role in the emergence of perioperative peripheral nerve injury. Both general and regional anaesthesia may potentially cause peripheral nerve injury with different mechanisms including compression, stretch, direct nerve trauma and local chemical toxicity [49]. An extensive retrospective review reported the incidence of perioperative PNI at 0.03%. The same review demonstrated that general anaesthesia and epidural anaesthesia have associations with nerve injury, but peripheral and spinal nerve blocks do not [37]. The ulnar nerve is the most commonly compromised nerve under anaesthesia [50]. Predisposing factors that make patients more susceptible to nerve injury are diabetes mellitus, hypertension, tobacco use, arthritis, obesity and low body weight [28, 37]. Except for compression injuries secondary to improper patient positioning, direct needle trauma may be the main cause of the anaesthesia-related peripheral nerve injury. There are various risk factors that affect the risk of nerve trauma with regional anaesthesia. Needle may damage the nerve fascicles directly, and damaged nerve vessels and existing extraneural or intraneural haematoma may compromise nerve fascicles [51]. Injecting the local anaesthetic into a fascicle is the main source of peripheral nerve block-related nerve injury. Intrafascicular injection traumatizes the nerve, damages perineurium and results in the loss of protective environment within the fascicle [37, 51–53]. Epinephrine when combined with local anaesthetics tends to cause local vasoconstriction, but its role in causing nerve injury is still controversial [54]. High-pressure local anaesthetic injection may damage neuronal microvasculature and cause neural ischemia [55]. Both neuraxial block and peripheral nerve blocks' needle type is associated with neuronal injury risk. Nerve puncture with pencil-point or Tuohy needles causes a similarly high degree of injury [56]. Human studies could not demonstrate the difference between neurostimulation-guided or ultrasound-guided nerve blocks in terms of nerve injury [51].

Fortunately, complications of neuraxial blocks are rare. A large-scale research study reported that the incidence of neuraxial complications is 0.0075%, and 67% of them results in permanent injury. The most common complications are spinal hematoma, cauda equina syndrome, purulent meningitis and epidural abscess. Studies mentioned that the risk of spinal haematoma is higher with epidural anaesthesia compared to spinal anaesthesia [57]. The risk is higher in patients who have coagulation abnormalities, advanced age, female gender, concurrent spinal stenosis or preexisting neurological diseases [58].

Improper positioning is another cause of anaesthesia-related perioperative peripheral nerve injury. Wrong patient positioning increases the compression pressure on nerves which are superficial or in close proximity to a bone. For example, the ulnar nerve is a superficial nerve which is in the vicinity of the medial epicondyle of the humerus, or the peroneal nerve is near the fibular neck. Additionally, excessive tractions of the nerves may be another injury mechanism (excessive traction of the shoulder causes brachial plexus injury). Anaesthesiologists should be aware of the body position and its association with nerve injury (e.g., lithotomy and femoral nerve injury, lateral decubitus position and peroneal nerve injury, taping the shoulders and brachial plexus injury) [41]. The American Society of Anaesthesiologists published a practice guideline for prevention of positioning-related peripheral nerve injury. The guideline recommends careful positioning of the patient, protective padding, padded arm boards and avoidance of contact with hard surfaces. Specifically, the guideline advised that arm abduction should be limited to  $<90^\circ$  in the supine position to protect brachial plexus, neutral forearm positioning or supination of the hand should be done with padding in the supine position to protect ulnar and median nerves, flexion of the elbow should be limited to  $<90^\circ$ , appropriate padding should be applied in lithotomy in lateral and prone positioning, and hip flexion should be  $<120^\circ$  in lithotomy positioning [59].

### **6.3. Tourniquet-related nerve injury (TRNI)**

Despite its rare but devastating side effects, pneumatic surgical tourniquets are widely used in orthopaedic and plastic surgery because bloodless operative site is very important for optimum surgery. Pathophysiological mechanisms of the TRNI include mechanical compression and neural ischemia [60]. Mechanical compression causes microvascular congestion, inadequate perfusion, axonal degeneration and transient loss of innervation function [61]. These effects usually start within 2–3 hours. Even when the insufflation pressure is appropriate or tourniquet time is short, the potential for nerve injury still persists [62]. Fortunately, when standard recommendations are followed, major neurological deficit is rare. The incidence of permanent injury is 0.032% [63]. If the mechanical stress is the major pathological factor in TRNI, it is recommended that the placement of the tourniquet be as proximal as possible to the limb to enlarge the limb circumference with muscle mass with the aim to protect the nerves [64].

### **6.4. Regions with higher risk of nerve injury**

In some body regions, nerves lay superficial and have close proximity with hard tissue. In these superficial regions, nerves have a narrow diameter that makes them more susceptible to the injury. These sites include the wrist (ulnar nerve), posterior triangle of the



neck (spinal accessory nerve (SAN)), posterior of the knee and popliteal fossa, fibular head (peroneal nerve), elbow and groin (ilioinguinal, iliohypogastric nerve) [8].

## 7. Peripheral nerves and clinical presentations of injuries

Based on the results of a large clinical experience report, the median nerve is the most commonly injured nerve among the iatrogenic nerve injuries. It is followed by the accessory nerve, radial nerve, common peroneal nerve (CPN), ulnar nerve and femoral nerve [41]. The diagnosis of iatrogenic nerve injury is easy. An asymptomatic patient starts to complain about neurological symptoms after a surgical intervention. Neurological symptoms may include sensory deficits or motor movement limitations. Sensory symptoms may include anaesthesia, paraesthesia, hypoesthesia, hyperesthesia and pain. Motor limitations may include paresis and paralysis. Autonomic dysfunction or neuropathic pain may be observed depending on the type of nerve and the injury process [49].

### 7.1. Lingual and inferior alveolar nerves

The lingual nerve is a sensory nerve, the inferior alveolar nerve is both sensory and motor, and two of them are branches of the mandibular nerve. These nerves are mostly injured during orodental practices such as exodontic and endodontic procedures, dental implants and injection, and osteotomy. Injury symptoms are mostly similar to those mentioned above. Paraesthesia is a common symptom experienced by patients with these nerves injuries. The common cause of iatrogenic paraesthesia is extraction of third molars and dental injections. Twenty-five per cent of patients with iatrogenic paraesthesia suffer from permanent conditions and 75% regain normal sensation spontaneously without further treatment within 6–8 weeks [65, 66]. Spontaneous recovery may be prolonged up to 24 months. Microsurgery may be indicated in the following cases: confirmed transection of a nerve, total anaesthesia of the affected area 2 months after the trauma, lack of protective reflexes (on biting or burning of the tongue or lower lip) 2 months after trauma, dysaesthesia. Considerable functional improvement after surgery may be seen, but regaining normal sensation is not always possible [67].

### 7.2. Laryngeal nerves

The internal branch of the superior laryngeal nerve (IBSLN) provides general sensation for the tissue superior to the vocal cords. The external branch of the superior laryngeal nerve (ESBLN) innervates cricothyroid muscle and contributes to innervation of the pharyngeal plexus. The ESBLN is closely related to the superior thyroid vascular pedicle, and this anatomic relationship makes the nerve vulnerable to iatrogenic injuries. The recurrent laryngeal nerve (RLN) supplies four intrinsic muscles of the larynx except cricothyroid muscles and supplies the mucosa of vocal cords and subglottis. Although controversy still exists, exploration and dissection of the nerve are still recommended to avoid nerve injury during surgery. Thus, surgeons should identify some landmarks (inferior thyroid artery, tracheoesophageal nerve, Berry's ligament, Zuckerkandl's tubercle) which are closely related to the RLN to help protect the nerve from injury [68].

Iatrogenic laryngeal nerve injury is mostly seen after anterior neck surgery (thyroid, parathyroid, anterior cervical spine surgeries, carotid endarterectomy). While advanced neurophysiological monitoring techniques are performed during anterior neck surgery, clear visualization of the nerve during surgery is still more important to prevent nerve injury [69]. Symptoms of laryngeal nerve injury are difficulty in speaking, difficulty in swallowing, hoarseness and breathing problems (if the injury is bilateral) [68]. Laryngeal electromyography (EMG) has been the gold standard in the diagnosis of laryngeal nerve injuries. Iatrogenic RLN injury was found in 0.3–13.2% of the cases, and superior laryngeal nerve (SLN) injury occurred in less than 5% of the cases. Transient vocal cord palsy recovers within 6 months. Permanent vocal cord palsy, which is not recovering within 1 year, occurs in 0.4 and 2.8% of the cases [70–76].

The treatment of RLN injury includes medicines (neurotrophic agents, glucocorticoids or vasodilators), ultrashort wave therapy, voice training, vocal cord injections and reinnervation methods (decompression, end-to-end anastomosis, implantation of an ansa cervicalis nerve-muscle pedicle). Recent treatment methods include thyroplasty, laser arytenoidectomy and cordectomy. The recovery success of the RLN depends on early diagnosis and early exploration of the nerve [77–79].

The treatment of SLN injury includes voice therapy, type 1 or 4 thyroplasty and reinnervation using nerve muscle pedicle technique. There are no studies which extensively investigated the success of these therapeutic methods for SLN injury [80–83].

### **7.3. Facial nerve**

Published facial nerve injury rates in oral surgical procedures vary from 2 to 25% and 0.6 to 3.7% in primary tympanomastoidectomy. Secondary tympanomastoidectomy procedures doubled the risk of iatrogenic facial nerve injury (IFNI) (4–10%). In an epidemiologic report, oral maxillofacial surgery was the most common procedure that caused iatrogenic facial nerve injury. Temporomandibular joint reconstruction, mastoidectomy, parotidectomy and rhytidectomy are the most risky procedures in terms of IFNI. Hemifacial paralysis is the most prevalent pattern of IFNI. When IFNI is diagnosed in a patient, he/she must be referred for facial nerve exploration immediately. Reconstruction should be performed within 4–6 months after surgery to avoid severe atrophy of the mimetic muscles that occurs 12 months after denervation. Currently, no medical treatment exists for facial nerve injury. Systemic corticosteroids have minimal contribution to the recovery, and the mainstay of treatment is surgery. Surgical options include direct repair, cable nerve grafting and nerve substitution techniques. Residual weakness and synkinesis are common results of facial nerve repair. Common factors restricting functional recovery include older age, long grafts and extended delay between injury and repair [84–89].

### **7.4. Spinal accessory nerve**

Cervical lymph node biopsy is the most common cause of iatrogenic spinal accessory nerve (SAN) injury, and the incidence after this procedure varies between 3 and 10%. SAN injury results in the loss of trapezius muscle motor function and weakness of the shoulder abduction, dropping of the shoulder, winging scapula and shoulder pain. Although SAN is a motor

nerve, patients often describe a sharp, electric shock pain during the procedure. Spontaneous recovery of SAN injury is very rare. If the lesion is left untreated, pain or functional deficit will occur in 60–90% of patients. The surgical repair procedures include end-to-end anastomosis and nerve grafting. Early reconstruction surgery (within 3–6 months of injury) is recommended to avoid permanent functional deficit of the trapezius muscle. However, positive functional results can still be expected within 9 months of the injury since the distance to the target muscle is short [40, 89–92].

### **7.5. Brachial plexus**

The anatomical features of the brachial plexus make it susceptible to iatrogenic injuries. Brachial plexus is superficial, lies between mobile bones and has a limited range of movement between the clavicle and the first rib. Iatrogenic injuries may be induced by compression, stretching or direct damage. Median sternotomy during cardiac surgery, lateral decubitus positioning, shoulder surgery, arm abduction and shoulder displacement are the iatrogenic causes of the injury. Motor dysfunction is the major clinical presentation that depends on the injury level. Surgical treatment options include neurolysis, nerve suture, nerve grafting and neurotization. Timing of surgery differs according to the injury type. Laceration injuries should be explored acutely, blunt injury reconstruction may be performed within 2–3 weeks of the injury and closed traction injury is operated within 4–5 months of the surgery [49].

### **7.6. Median nerve**

As demonstrated in a comprehensive research study, median nerve is the nerve most commonly susceptible to iatrogenic nerve injury [42]. Median nerve is mostly harmed during carpal tunnel release procedures. Surgeon's knowledge on skin landmarks may diminish the nerve damage. Median nerve injury presents with paraesthesia in the palmar side of the fingers, weakness of abduction, opposition of the thumb and forearm being kept in supination. Near the motor deficit, patient may complain about electric-like shooting pain. Early exploration and treatment are recommended before chronic pain syndrome is manifested [49].

### **7.7. Ulnar nerve**

Ulnar nerve injury is the most common perioperative peripheral nerve injury because the ulnar nerve is superficial and in close proximity to the medial epicondyle of the humerus. Subclinic neuropathy is the most common presentation. Tingling, numbness along the little finger, weakness of abduction and adduction of the fingers are usual clinical presentations [49].

### **7.8. Radial nerve**

Radial nerve lies along the spiral groove of the humerus, and this location is the most injured site of the nerve by dislocated humeral fracture. Open reduction and fixation of the fracture may cause iatrogenic nerve injury. Kirschner wire placement for radial fractures can penetrate the nerve. Thus, mini-incisions for surgical procedures rather than percutaneous procedures are preferable to protect the nerve. There are numerous treatment options for radial

nerve repair. None of them has proven better outcomes than others. However, radial nerve has a perfect recovery profile after reconstruction [49].

### **7.9. Phrenic nerve**

The phrenic nerve supplies diaphragm that originates from cervical nerve roots and descends through the thorax. Left phrenic nerve lies within the pericardium. The phrenic nerve paralysis occurs mostly after cardiothoracic surgery with an incidence of 1.4–7%. In addition to trauma, pericardial crushed ice placement is another cause of iatrogenic nerve injury in cardiac surgery. Elevated hemidiaphragm, lower lobe atelectasis and poor respiratory effort are the clinical presentations of the paralysis. Cold injury and internal mammary artery dissection increase the risk of phrenic nerve injury. Even if it takes weeks and months, the prognosis of phrenic nerve injury is good. Most patients recover within 1 year eventually [93–95].

### **7.10. Inguinal nerves**

The ilioinguinal, genitofemoral and iliohypogastric nerves are cut, coagulated, sutured or incorporated into a mesh during open and endoscopic inguinal hernia repairs. These nerves may also be injured during laparotomy. Inguinal nerve injury during hernia repair occurs in 0.5–2% of the procedures. Clinical presentation of these nerve injuries includes a sharp, burning pain radiating to the suprapubic area, labia or scrotum, paraesthesia over the same areas and pain relief after infiltration of a local anaesthetic. Symptoms are aggravated by stretching, coughing, sneezing and Valsalva manoeuvres. Pain is diminished in more than 90% of the patients after neurectomy and excision of the injured nerve [96–100].

### **7.11. Femoral nerve**

Postoperative hematoma, cement extrusion, trauma from retractors, bone or prosthesis malpositioning and lithotomy position with extreme abduction of thighs are the main causes of iatrogenic femoral nerve injury. Deep pelvic surgery and abdominal surgeries are procedures that are most commonly implicated in iatrogenic femoral nerve injury. In these operations, the common risk factor is compression by retractor blades. Thin subcutaneous fat layer, surgical duration longer than four hours, poorly developed rectus muscle, narrow pelvis and self-retaining retractors are the risk factors for femoral nerve compression. Clinical presentations of femoral nerve injury include loss of sensation at the front of the thigh, weak hip flexion and loss of knee extension. Although severe nerve injuries need long nerve grafts, femoral nerve reconstructions result in good functional recovery [101–103].

### **7.12. Sciatic nerve**

Sciatic nerve injury manifests itself as paralysis of the hamstring muscle, foot drop and impaired sensation below the knee except medial regions. The lithotomy, frog leg and sitting positions cause perioperative nerve injury by stretching the nerve [49]. Sciatic nerve injuries are mostly reported as a complication of total hip arthroplasty with an incidence of 0.16–8%. Hip dysplasia, posterior approach, revision surgery (3.2%), limb lengthening, female gender

and younger age are the primary risk factors of nerve injury. The most common mechanisms include tension, direct trauma by retractors, compression by postoperative hematoma, direct lacerations and sutures. Sciatic nerve injury occurs in 1.7% of hip arthroscopies. Complete injuries without therapy cause 100% limb disability [104–108]. Results of operative treatments are mixed. A large series of sciatic nerve repairs reported that tibial division recovery is better than peroneal division, and outcomes at the thigh are better than at the buttock [101].

### 7.13. Common peroneal nerve

The common peroneal nerve (CPN) injury presents with loss of dorsiflexion and eversion of the foot (equinovarus deformity). Sensory impairment occurs in the anterolateral region of the leg. Iatrogenic injuries are related to high tibial osteotomies (HTO) (4.9%) and total knee arthroplasties (TKA) (0.3–9.5%). Revision surgeries, preoperative valgus deformity, rheumatoid arthritis, history of previous HTO, prolonged tourniquet time and history of laminectomy are the risk factors of perioperative CPN injury [109–113]. Lithotomy and lateral position are the nonsurgical perioperative risk factors for CPN injury which is associated with fibular head compression. Full recovery rates of partial nerve injury vary between 76 and 87%, and complete injury recovery is seen in 20–35% of the cases [101]. Surgical treatment is indicated if no evidence for recovery is observed.

## 8. Functional assessment and management of peripheral nerve injury

Clinical presentations of peripheral nerve injury usually include pain, dysaesthesia and partial or complete loss of motor and sensory functions. Evaluation of the injury starts with complete history and physical examination. Diagnosis is established through electrodiagnostic assessment and radiological studies. Treatment options are performed according to the wound characteristics at the appropriate timing in terms of the injury mechanism after all examinations.

Physical examination should involve detailed assessment of motor and sensory deficits. Moving and static two-point discrimination, sharp and dull discrimination, grading of grip and pinch strength should be tested and recorded preoperatively. Subsequent to these procedures, peripheral tissues of the injury site (soft tissue, vascularization) should be examined. Tinel's sign over the course of the injured nerve will be positive. It refers to paraesthesia elicited by lightly tapping over the suspected location. Tinel's sign is elicited by regenerating axonal growth [114].

The timing of functional assessment according to the injury type is an important issue for diagnostic success. Optimum timing for electrodiagnostic studies varies between injury types. The formation of Wallerian degeneration is the main point of distinction of the neuropraxia, axonotmesis or neurotmesis. Initial electrodiagnostic studies 7–10 days after an acute injury may be helpful to localize the lesion and to distinguish conduction blocks from axonotmesis. Electrodiagnostic studies, which are performed 3–4 weeks after surgery, provide more information about the lesion because fibrillation potentials may not appear until this time [115]. Electrodiagnostic studies are mostly useful during intraoperative management



while checking an action potential distal to the injury. They are also useful to distinguish the intact fascicle and neuroma intraoperatively. Electrophysiological procedures have a critical role in monitoring recovery and determining neuronal reinnervation 2–4 months after nerve surgery [114].

Electromyography (EMG) demonstrates the electrical activity of a muscle and is useful for detecting injuries of efferent peripheral neuron and motor unit. Reduced number of functional axons after an injury causes EMG abnormalities. In neuropraxia, it demonstrates normal or decreased recruitment. However, following lesions causing axon loss, EMG demonstrates abnormal activity such as fibrillation and positive sharp waves. EMG may be normal immediately after axonotmesis and demonstrates abnormal activity after 10–14 days. The onset of the fibrillations depends on the length of the distal nerve stump. Fibrillation development with short stumps may take 10–14 days, and for longer stumps, it may take 21–30 days (e.g., ulnar-innervated hand muscles in a brachial plexopathy) [115].

Nerve conduction studies (NCS) assess both motor and sensory functions of the nerve via a voltage stimulator. The evoked response is recorded from a surface electrode overlying the muscle (motor response) or nerve (sensory response). NCS is used initially to demonstrate the presence of conduction block [13]. In pure neuropraxic injuries, motor response failures occur immediately and conduction is detected to be normal distal to the lesion. Electrodiagnostically complete axonotmesis and complete neurotmesis demonstrate the same results. Immediately after axonotmesis motor conduction studies show the same pattern as neuropraxia until Wallerian degeneration has occurred. Typically, Wallerian degeneration occurs 9 days after injury, and it becomes possible to distinguish neuropraxia and axonotmesis. After this time, amplitude of the motor response falls and later responses are absent in both proximal and distal of the lesion [115]. Consequently, EMG and NCS should be used complementarily to define the characteristics of the injury (complete or incomplete injury, localization, injury age, injury grade, prognosis and postoperative recovery) [49].

Radiological studies have a limited role in diagnosing peripheral nerve injuries. However, they may be used complementary to the electrodiagnostic studies. Mostly magnetic resonance imaging (MRI) and high-resolution ultrasound are used for peripheral neuroimaging. Both are helpful to determine the exact site of the lesion particularly when electrodiagnostic studies are insufficient [49].

## **9. Treatment strategies of peripheral nerve injury**

The recovery time of the injured nerve depends on various external factors including most importantly early nerve exploration and repair. However, it should be known that axonal regeneration rate is as slow as 1–2 mm per day and there is no treatment to accelerate this process [15]. The irreversible motor unit degeneration starts 12–18 months after denervation of the muscle but may persist for 26 months [116]. Recovery of sensory regeneration may take longer. Additional injury at target muscles or an injury in peripheral supportive tissue delays the recovery more than usual.

The features of the injury define the type or timing of the surgical nerve repair. There are three types of wound including tidy, untidy and closed traction injuries. The tidy wound may be made by a glass or a scalpel, which has sharp edges and primary repair is a preferable treatment option. Untidy wound samples are open fractures or gunshot wounds with extensive tissue damage and infection and cannot be repaired immediately. Closed traction injuries have retracted and damaged nerves, vessels and peripheral supportive tissues. Closed traction injuries have the worst outcomes of all wounds.

Nerve exploration and repair indications are paralysis around the injured nerve, closed injury with supportive tissue damage, open injury requiring open reduction and internal fixation, nerve lesions with arterial damage, traction injuries to the brachial plexus, declining nerve function after diagnosis, failure of neurological improvement, failure to improve after a conduction block within 6 weeks of the injury and persistent pain or neuroma formation [4].

### **9.1. Direct nerve repair**

Direct nerve repair with microsurgical techniques is still a gold-standard treatment method for axonotmesis and neurotmesis injuries [14]. Direct suturing repair without grafting is used for short nerve deficits (<5 mm). Larger deficits require nerve grafting. Repair of a large gap without grafting exhibits excessive tension and produce poor outcomes. In terms of recovery for larger gaps, repair with nerve grafting has better outcomes compared to primary repair without grafting [4].

### **9.2. Fibrin glue**

Fibrin glue enables primary sutureless repair with an adhesive. Repair with fibrin sealants ensures shorter recovery time, less fibrosis and decreased inflammatory reactions. Studies do not report any difference between fibrin glue and direct suturing in terms of axonal regeneration, fibre alignment and nerve conduction velocity recovery [117]. The most important advantage of the fibrin glue is quick and easy application in emergency conditions whenever there is absence of experienced surgeon for nerve repair.

### **9.3. Nerve grafts**

Autologous nerve grafts are the gold-standard option in peripheral nerve repairs. As reported in the literature, autologous nerve grafting has better recovery results in long nerve deficits (>3 cm), more proximal injuries and critical nerve injuries [15]. Donor nerve grafts are extracted from expandable sensory nerves such as sural and medial antebrachial nerves. Autologous nerve grafting has best results because it has necessary materials for nerve regeneration like Schwann cells, basal lamina, neurotrophic factors and adhesion molecules [2]. Despite its superior results, using autologous nerve grafts has some limitations including limited tissue availability, necessity for second surgery, the graft, donor-site morbidity, loss of nerve function and potential difference in tissue size. Allograft nerves that are collected from a cadaver or donor for nerve grafting are other options. Donor allografts contain viable donor Schwann cells, and immunosuppressive therapy is needed for 18–24 months to inactivate these cells for sustained

regeneration. Immunosuppressive therapy has many side effects including opportunistic infections and tumour formation. Cadaveric nerve allografts are used in patients who have inadequate autologous nerve grafts. The recovery results are good, but the process is too expensive and requires experience to perform [118–121].

Currently, scientists focused their research on acellular human nerve allografts with the aim to eliminate the need for immunosuppressants. The decellularization process is performed using chemical detergents, enzyme degradation or irradiation [122]. Acellular nerve grafts are removed from Schwann cells and myelin, but the internal neuronal structure and extracellular matrix (collagen, laminin and growth factors) are preserved [123]. Regeneration process with acellular allografts involves host's migrated Schwann cells. Thus, even when acellular nerve grafts show good outcomes in trials, they are still insufficient in long nerve deficit repairs. In future, acellular grafts supplemented with seed cells, and growth factors may improve the surgical repair outcomes of large gap peripheral nerve injuries [124].

#### **9.4. Nerve conduits**

In recent years, research efforts have focused on the development of conduits as an alternative treatment especially for larger defects. Nerve conduits serve as a bridge between the proximal and distal stumps of the injured nerve and provide a scaffold for axonal regeneration. The most important advantage of a conduit is the ability to provide an ideal microenvironment for neuronal recovery. For this purpose, an ideal nerve conduit should have properties like biocompatibility, permeability, flexibility, biodegradability, compliance, neuroinductivity and neuroconductivity with appropriate surface [137, 138].

Conduits are categorized into two groups according to their materials as biological and synthetic conduits.

Biological nerve conduits include autologous arteries, veins, muscle, human amniotic membrane and umbilical cord vessels. Major advantages of biological conduits are non-activation of foreign body reaction, biocompatibility and enhanced migration of supportive cells. These biomaterials have been widely used for repair of short gap (<3 cm) nerve injuries, and the outcomes were consistent with those of nerve grafts [125–127, 138].

Synthetic nerve conduits include degradable and nondegradable conduits. Nondegradable nerve conduit materials include silicone, elastomeric hydrogel and porous stainless steel. Reconstruction with these materials is successful, but the possibility of foreign body reaction, scar tissue formation secondary to inflammation, lack of stability and the inflexible structure limit extensive use of them. Another disadvantage is the requirement of a second surgery for conduit removal.

Commonly used degradable conduit materials include collagen, polyesters (e.g., polyglycolic acid (PGA)), chitosan, polylactic acid (PLA) and hydrogel. These materials induce only minimal foreign body reaction, and several investigators reported effective nerve regeneration with these conduits [128]. Particularly, collagen conduits have shown comparable results with autologous nerve grafts in animal studies. There are many Food and Drug Administration (FDA) approved collagen-based conduits such as NeuraGen, NeuroFlex, NeuroMatrix, NeuroWrap and NeuroMend. Researchers observed that collagen conduits are resorbable, flexible, and

cause minimal scar formation, allow nutrient transfer and provide suitable environment for nerve regeneration without any compression neuropathy. Over time, the material choice for nerve conduits shifted towards the use of more biocompatible synthetic polymers. Examples of these polymers are polylactic acid (PLA), polyglycolic acid (PGA), poly-caprolactone (PCL) and poly-lactide caprolactone (PLCL). Neurotube is a PGA nerve conduit, and Neurolac is a PLCL conduit. Neurotube was designed for gaps between 8 mm and 3 cm and is resorbed within 6–8 months. Neurolac is available as a tube with a length of 3 cm. In clinical trials, PGA conduits had comparable results with gold standards in the treatment of gaps up to 20 mm. A human study reported fistulization and neuroma in hand nerve surgery with PLCL conduits. Fibrin, gelatin, keratin and silk are other biopolymer conduit materials that are still under experimental evaluation [137, 138].

Studies have concluded that none of the experimental materials used for nerve conduits performed better than nerve grafts. However, observations showed that some of the properties make nerve conduits more useful (see **Table 1**). Conduits developed in the future should have a combination of aforementioned favourable properties.

9.5. Growth factors

Neurotrophic growth factors which are naturally released from injured nerves are used during nerve repair interventions. Studies about nerve repair pathophysiology reported that these growth factors act as cell regulators and they are all essential. Several studies showed that all these neurotrophins promote peripheral nerve regeneration [132, 133]. Additionally, neurotrophic growth factors promote both outgrowth and survival of motor and sensory neurons. Principal neurotrophic factors used for peripheral nerve regeneration are presented in **Table 2**. In experimental models, growth factors for nerve regeneration are generally used with nerve conduits.

9.6. Cell-based therapy

The limitations of present therapies are slow nerve regeneration and insufficient filling of large nerve gaps. To overcome these limitations, cell-based therapy was designed to provide supportive cells to the lesion site with the aim to accelerate nerve regeneration. Supportive

Should not harm peripheral tissue of the injury site
Resorbable
Limiting fibrous tissue infiltration
Allowing nutrient transfer with pores
Protein release (laminin/fibronectin)
Appropriate internal diameter to allow nerve regeneration
Release of neurotrophic factors
Allowing electrical conductance

**Table 1.** Desired features of the nerve conduits [137].

Neurotrophic factors	Effect
Nerve growth factor (NGF)	Survival signalling, neurite outgrowth
Glial cell line-derived neurotrophic factor (GDNF)	Sensory regeneration
Brain-derived neurotrophic factor (BDNF)	Positive modulation of peripheral nerve myelination
Neurotrophin-3 (NT-3)	Negative modulation of peripheral nerve myelination
Neurotrophin-4/5 (NT-4/5)	Survival of sensory neurons
Ciliary neurotrophic factors (CNTF)	Survival of motor neurons

**Table 2.** The effects of neurotrophic factors in peripheral nerve regeneration [137].

cell additions are combined with nerve grafts or conduits. Most extensively studied therapeutic models have included Schwann cells (SCs), but scientific improvements were achieved with different types of stem cells as well. Cell-based therapy is performed with stem cells owing to their self-renewal ability and capacity for differentiation into specialized cell types. Investigations on cell-based therapy are still in the preclinical level except some trials on Schwann cells [139]. Stem cells used for nerve repair interventions are mentioned in **Table 3**.

Schwann cells, bone marrow-derived mesenchymal stem cells (BMSCs), adipose-derived mesenchymal stem cells (ADSCs) and pluripotent stem cells are the primary cell types which are used in research studies. First of all, SCs are the most important and first-choice seed cells because they are the primary functional cells of the nervous system. SCs have a crucial role in nerve regeneration by producing neurotrophic factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor, platelet-derived growth factor and neuropeptide Y. In addition to being a supply for growth factors, SCs are capable of proliferation, immune modulation, remyelination and migration. All of these enhance repaired nerve healing. In cell-based therapies, neural crest cells are the main source of Schwann cells. SC seeds transplanted in a nerve conduit enhance axonal regeneration, but SC seeds have some disadvantages such as slow expansion to large numbers and being hard to obtain [129, 130, 140].

Embryonic stem cells (ESCs)
Neural stem cells (NSCs)
Bone marrow-derived stem cells (BMSCs)
Adipose-derived stem cells (ADSCs)
Skin-derived precursor stem cells (SKP-SCs)
Foetal-derived stem cells
Hair follicle stem cells (HFSCs)
Dental pulp stem cells (DPSCs)
Muscle-derived stem/progenitor cells (MDSPCs)
Induced pluripotent stem cells (iPSCs)

**Table 3.** Stem cells studied in peripheral nerve repair [139].



Embryonic stem cells (ESCs) have preferable advantages such as providing an unlimited source of cells, good differentiation potential and long-lasting proliferation capacity. However, ethical concerns are the major problem when these cells are used for transplantation. NSCs have the ability to differentiate into neurons and glial cells, but their use is limited because harvesting of these cells is difficult and there is a risk for formation of neuroblastoma. Bone marrow-derived stem cells (BMSCs) have the potential to differentiate into SC-like cells (BMSC-SCs). However, studies showed that differentiation potential of BMSCs is not as strong as NSCs. Also, harvesting procedure is painful and results in a lower cell fraction compared to other stem cells. Harvesting of ADSCs is minimally invasive and results in a high cellular yield. ADSCs can differentiate into SC-like cells and release BDNF, NGF and vascular endothelial growth factor (VEGF). These factors facilitate recruitment of endogenous SCs. The most important factor limiting the use of ADSCs is the potential to differentiate into adipocytes. Studies on BMSC-SCs and ADSC-SCs have yielded promising results [131, 140].

Foetal stem cells can be derived from amniotic fluid, amniotic membrane, umbilical cord and Wharton's jelly. Both amniotic tissue-derived stem cells (ATDSCs) and umbilical cord-derived mesenchymal stem cells (UC-MSCs) have differentiation and proliferation potential. ATDSCs also exhibit strong angiogenic potential and cause augmented neuronal injury perfusion. Tumorigenesis is one of the important side effects of UC-MSCs secondary to their high proliferation potential. Wharton's Jelly MSCs show specific mesenchymal features like generating neurotrophic factors such as NGF, BDNF and NT-3. Major advantages of foetal-derived stem cells are easy access and less immunoreactivity. Ethical issues are the most important disadvantage of foetal-derived stem cells. Skin-derived precursor stem cells (SKP-SCs) are found in the dermis and can differentiate into many kind of cells like neurons and glial cells. It is reported that SKP-SCs accelerate nerve regeneration. Hair follicle stem cells (HFSCs) have a unique feature of differentiation into SCs directly without any genetic intervention. Animal studies reported improved nerve repair with HFSCs. Several drawbacks associated with the stem cells have led to research efforts for alternative cells like induced pluripotent stem cells (iPSCs). iPSCs showed enhanced neuronal regeneration, but tumorigenicity, need for immunosuppression and chromosomal aberrations limit their use [139, 140].

As a result, ideal cells to be used for neural regeneration should have the properties of being suitable for easy harvesting, not requiring immunosuppression, being able to integrate to the injury site and being non-tumorigenic. And the success of a cell-based therapy depends on the transplanted cell's ability to differentiate into Schwann-like cells, to release neurotrophic growth factors and to induce myelination of axons. Schwann cell cultures have mostly shown acceptable results in experimental studies; however, they are not good enough and search for an ideal cell is still ongoing. Bone marrow-derived mesenchymal cells have also demonstrated favourable results with numerous advantages like easy harvesting, high cell viability and secretion of multiple trophic factors [139, 140].

Even though cell-based therapy is promising for future, it is already associated with certain limitations. The most important issue is cell transplantation safety, and the other is that cell preparations are time consuming. These delays might cause the most appropriate intervention time for neuronal repair to be missed.

### 9.7. Other methods

Freeze-thawed muscle graft, nerve transfer and direct muscular neurotization are the other surgical methods for nerve repair. In the nerve transfer surgery, the uninjured nerve is transferred to the distal stump of the injured nerve. During the direct muscular neurotization, the avulsed end of the nerve is implanted into the muscle directly. All of these techniques still need further improvement [133–136].

## 10. Conclusion

Microsurgical direct nerve repair is still gold standard for peripheral nerve repair whenever possible with a tension-free and early repair. It should not be forgotten that nerve repair that would give the optimum result requires healthy supportive tissue. If there is large nerve deficit, the autologous nerve graft is accepted as the gold standard. Second surgery, potential for neuroma formation and loss of donor nerve function are the main disadvantages of autologous nerve grafting. And all these limitations cause to perform acellular human nerve grafts. Acellular grafts have promising results but are still insufficient for large nerve deficits. At this stage, nerve conduits which stand out with the formation of an ideal microenvironment in the large nerve defects are increasingly foreground. But performing successful results with nerve conduits still requires combination of pharmacological and molecular therapies. Researches should focus on both axonal regeneration and achieving optimum microenvironment. In this context, it is important to manipulate Schwann cells. Because SCs provide supportive cell proliferation, remyelination and growth factor supply. Studies about performing SCs-like cells become more important because harvesting SCs is not an easy and safe procedure. BMSCs and ADSCs have promising results, but tumorigenicity, need for immunosuppression and long-time need for cell preparations limit widely accepted clinical use of stem cells. Recent studies focus on manipulation of SCs to improve their contribution to nerve regeneration by increased motility, ability of differentiation and producing neurotrophic factors.

In conclusion, the combination of genetically modified Schwann like cells and conduits or acellularized grafts as three-dimensional structured scaffolds will finally achieve optimum functional recovery after peripheral nerve injury.

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